PATENT
Docket No.: **19603/3541 (CRF D-2694A)**

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants	:	Hyman et al.
Serial No.	:	10/001,643
Cnfrm. No.	:	2817
Filed	:	October 31, 2001
For	:	IN VIVO MULTIPHOTON DIAGNOSTIC DETECTION AND IMAGING OF A NEURODEGENERATIVE DISEASE

Examiner:
E. M. Mercader

Art Unit:
3737

REQUEST FOR RECONSIDERATION

Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Dear Sir:

In response to the May 5, 2004, office action, reconsideration is respectfully requested.

The rejection of claims 1-34 under 35 U.S.C. § 103 for obviousness over U.S. Patent Publication No. 2002/0115717 to Gervais et al., ("Gervais") in view of U.S. Patent No. 6,280,386 to Alfano et al. ("Alfano"), and Christie et al., "Multiphoton Imaging of Alzheimer's Disease Neuropathology," *Society for Neuroscience Abstracts* 24(1-2):1219 (1998) ("Christie Abstract") is respectfully traversed.

Gervais relates to the use of amyloid-targeting imaging agents for imaging amyloid plaques *in vivo*. The amyloid-targeting imaging agents include an amyloid targeting moiety linked to a labeling moiety. The targeting moiety localizes the imaging agents to amyloid plaques, and the labeling moiety allows the imaging agents to be visualized by ultrasound imaging, computed tomography imaging, magnetic resonance imaging, nuclear medicine imaging, optical imaging, and elastography. Labeling moieties taught by Gervais for use in optical imaging include fluorescent or colored dyes. There is no suggestion in Gervais of using simultaneous multiphoton excitation, as claimed.

Alfano teaches an imaging system in which images of objects within tissue are enhanced by applying a contrast agent to a sample to be imaged, thereby forming a luminous

object. The tissue is illuminated and 2 image signals are recorded. These 2 image signals are subtracted to minimize an image component resulting from the tissue and to enhance the image component resulting from the luminous object. Alfano also fails to suggest the use of simultaneous multiphoton excitation.

The use of simultaneous multiphoton excitation in accordance with the present invention has a number of very important benefits. In particular, multiphoton excitation has a very high resolution capability, on the order of one micrometer (page 20, lines 26-29 of the present application), and can reach unprecedented depths (page 27, lines 15-18 of the present application). In addition to permitting high resolution imaging of living tissue, multiphoton excitation has the unique advantage of incurring only minimal photodamage or toxicity on the living tissue being imaged (page 25, lines 25-26 of the present application). These unique features of multiphoton excitation imaging make possible the detection and observance of certain Alzheimer's Disease-like lesions that are otherwise undetectable with prior art imaging technologies (page 25, lines 21-25 and page 46, lines 11-12 of the present application). Multiphoton excitation methods of imaging also provide the opportunity to evaluate a relatively large 3-dimensional reconstruction of the cerebral vasculature (page 32, lines 17-19 of the present application). Additionally, multiphoton excitation of fluorophores provides a method of imaging with improved background discrimination and reduces photobleaching of the fluorophores (page 12, line 19 to page 13, line 8 of the present application).

The Christie Abstract is cited to disclose the use of multiphoton imaging to analyze Alzheimer's Disease neuropathology. The abstract begins by citing a number of advantages if this approach were to be successful (Declaration of Watt W. Webb Under 37 CFR § 1.132 (attached hereto) ("Webb Declaration") ¶ 7). However, the Christie Abstract does not provide adequate information regarding how to use multiphoton excitation in imaging Alzheimer's Disease neuropathology (Id.). After discussing the advantages of such an approach (if successful), the abstract goes on to report the "first steps towards identification of multiphoton approaches to [Alzheimer's Disease] neuropathology" (Id.). The abstract then indicates that a technique has been developed for multiphoton visualization of amyloid deposition with a diffusable amyloid-binding fluorophore (Id.). This is stated to be useful in observing both plaques and tangles of Alzheimer's diseased brain (Id.). What is missing from the Christie Abstract, however, is anything approaching sufficient information to carry out this reported work (Id.).

Firstly, there is no description of how multiphoton excitation can be used to penetrate into the brain (Webb Declaration ¶ 8). As reported in the present application, it is necessary to provide a window in the skull or to "thin" the skull (Id.). If this is not done, multiphoton excitation radiation cannot penetrate the skull and image the brain (Id.).

There is also no description of what the actual wavelength of the multiphoton excitation emission is (Webb Declaration ¶ 9). Without this information, it is not possible to successfully utilize such excitation (Id.).

The Christie Abstract also fails to provide power level and pulse durations for the multiphoton excitation (Webb Declaration ¶ 10). If this information is not properly selected, it has been found that multiphoton excitation is ineffective in visualizing Alzheimer's diseased brain (Id.).

Another deficiency of the Christie Abstract is how low energy photons are to be summed (Webb Declaration ¶ 11). Again, if this is not done properly, multiphoton excitation will not be suitable for imaging Alzheimer's Diseased brain (Id.).

In view of all of these deficiencies in the Christie Abstract, those skilled in the art would not, based on the Christie Abstract, have been able to image Alzheimer's Disease neuropathology using multiphoton excitation (Webb Declaration ¶ 12).

Since Gervais and Alfano fail to teach or suggest the use of simultaneous multiphoton excitation of brain tissue for detection of neurodegenerative diseases and the Christie Abstract does not provide an enabling disclosure of how to carry out such multiphoton excitation, the rejection of claims 1-34 for obviousness over Gervais in view of Alfano and the Christie Abstract is improper and should be withdrawn.

In view of the foregoing, applicants submit that this case is in condition for allowance and such allowance is earnestly solicited

Respectfully submitted,

Date: September 7, 2004

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I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450, on the date below.

9/7/04 Date | Wendy L. Barry